Comprehensive Tuberculosis Testing for the Dermatologist

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ABSTRACT

Tuberculosis remains a noteworthy disease worldwide, rendering detection of latent tuberculosis of great importance. As healthcare workers, dermatologists should be aware of the available testing options and how they compare. In general, the tuberculin skin test has been around longer and, thus, there have been more studies performed on its sensitivity and specificity compared to interferon gamma release assays, which are newer to the market. The tuberculin skin test requires more office visits, takes longer to obtain results, is subject to healthcare worker bias, and can cause a booster phenomenon; whereas, interferon gamma release assays have a higher cost and less data available on their use in children under five years old. Both the tuberculin skin test and interferon gamma release assays fail to differentiate between recent and remote infections, have a low predictive value for active tuberculosis, and a lower sensitivity in people living with human immunodeficiency virus/acquired immunodeficiency syndrome. (*J Clin Aesthet Dermatol.* 2015;8(4):44–47.)

Tuberculosis (TB) remains an important worldwide disease with a third of the world's population being infected with TB. In 2012, the United States had 9,945 reported TB cases, which is a 5.4-percent drop from the previous year.[1] Despite this reduction, it is still pertinent for healthcare workers to be aware of such a widespread disease. The purpose of this article is to provide a concise and comprehensive review of TB testing strategies.

INDICATIONS FOR TESTING

Current TB testing includes tuberculin skin testing (TST) and interferon gamma release assays (IGRAs), which seek to identify latent tuberculosis infection (LTBI) in at-risk individuals who would benefit from LTBI treatment. Such populations include those at increased risk of new infection including those who are close contacts of individuals with active TB, casual contacts of individuals with highly contagious TB, and those with increased risk of exposure to patients with contagious TB, such as healthcare workers, prison employees, and homeless shelter employees. Individuals with increased risk of reactivation TB should also be tested. These individuals can fall into higher risk populations, such as those with human immunodeficiency virus (HIV), transplants, abnormal chest radiographs with apical fibronodular changes, renal failure on dialysis, and other immunocompromised states. Moderate risk populations should be tested under the age of 65 and include individuals with diabetes or taking glucocorticoids at 15mg/day or greater for one or more months. Further, there are some populations that have just slightly increased risk of reactivation TB. They should be tested under the age of 50 and include individuals who are underweight, smoke cigarettes, or have a chest radiograph with a solitary granuloma.[2]

TUBERCULIN SKIN TEST (TST)

Administration and interpretation. Traditionally, the TST, also known as the Mantoux test, was used to identify individuals with LTBI. The TST measures delayed-type hypersensitivity 48 to 72 hours after placement of the purified protein derivative (PPD).[3] The TST is performed in North America using PPD with a recommended dose of 5 tuberculin units (0.1mL). The Mantoux technique is performed by intradermal injection of PPD on the inner surface of the forearm (Figure 1), and the test is read based on the diameter of induration rather than erythema 48 to 72 hours after injection (Figure 2). In general, healthy individuals without risk of tuberculosis exposure are positive if their PPD measures 15mm or greater; individuals with increased risk of infection (such as healthcare

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workers) are positive if their PPD measures 10mm or greater; and immunocompromised individuals (such as HIV-positive patients) are positive if their PPD measures 5mm or greater.[4,2]

Repeat testing. If a PPD is found negative, three indications exist for repeat PPD testing: close contacts of patients with active tuberculosis, individuals with continued exposure, and to establish a baseline prior to serial testing (referred to as a "two step PPD"). Individuals working in healthcare should have a baseline two step PPD performed before they begin their yearly testing. The second PPD is completed 1 to 3 weeks after the first test. If the individual is negative, they most likely do not have LTBI. However, if they are positive on the second step, they are considered to have a "booster phenomenon." This phenomenon occurs in individuals who have a distant exposure to mycobacterial antigens (prior bacillus Calmette-Guérin [BCG] vaccination, nontuberculous mycobacteria exposure, or remote tuberculosis infection). The first PPD test causes an immunity memory, leading to a positive second PPD test. Individuals presenting with a booster phenomenon are considered infected and should be evaluated for LTBI treatment.[4,2]

Conversion. Individuals can also convert from a negative to positive TST test. Conversion refers to a positive TST up to eight weeks after a negative TST is found after recent exposure or a positive TST found in serial testing with ongoing exposure risk with a baseline negative TST. For either conversion or boosting phenomenon, the second TST is positive if the induration is 10mm or greater and has increased by 6mm or more since the last test.[2]

Limitations. In addition to the "boosting phenomenon," other limitations of the TST include reduced TST sensitivity due to malnutrition, severe TB disease, and immunodeficiency. The specificity of TST may also be decreased in areas where nontuberculosis mycobacteria are common or in individuals who have received the BCG vaccine after infancy. Further, the TST requires two healthcare visits, one for the PPD injection and the second for reading (four visits if a two-step test is performed). Additionally, reaction size measurement can be subject to interobserver variability. Another drawback is that if a TST is positive, it does not differentiate between recent and remote infections.[3]

Special populations. The TST is safe in children and can be used to diagnose TB or LTBI.[5] It is also safe in pregnant women and is only indicated if they are at increased risk of TB infection.[6] Individuals who are HIV-positive may have a false-negative test on TST because they lack the immune response capable of producing a positive test.[7] Thus, TST is not a very useful tool in TB diagnosis within this population.

Work-up. Individuals who have a positive TST should be further evaluated for LTBI treatment. Patients should have a chest radiograph to distinguish between LTBI and pulmonary TB. The radiograph is abnormal if it illustrates parenchymal abnormalities, especially (opacification) in

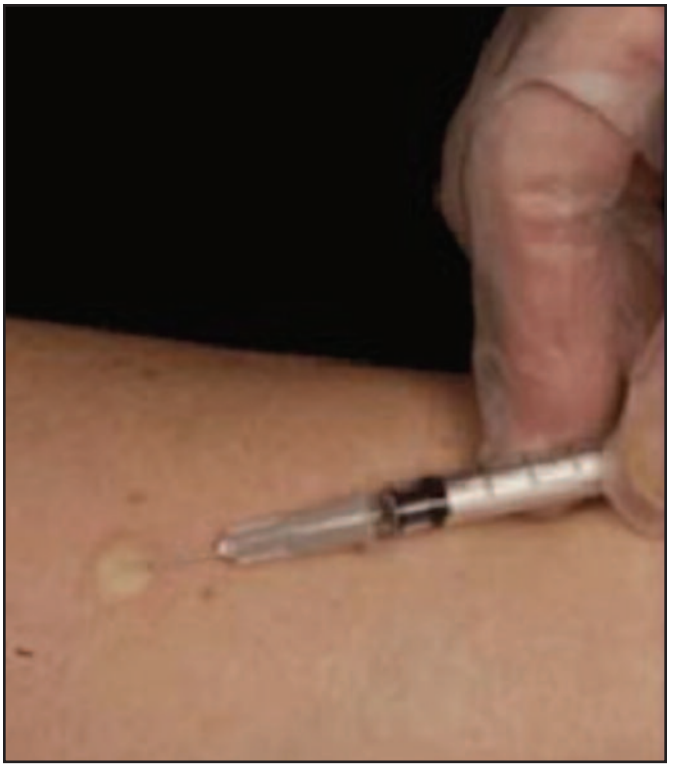

Figure 1. Intradermal PPD injection

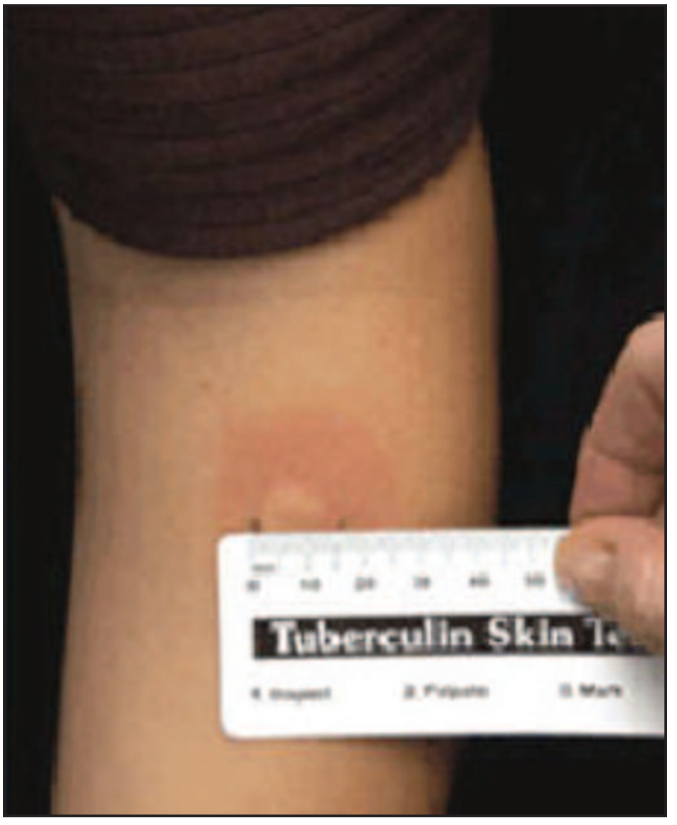

Figure 2. Measuring TST induration

TABLE 1. Timeline of interferon-gamma-release assay approvals

QuantiFERON TB	QuantiFERON Gold	QuantiFERUM Gold-in-Tube (QFT-GIT)	T-SPOT.TB Assay
2001	2005	2007	2008
Measures the cell-mediated immune response by incubating the serum with mycobacterial antigens and then determining the IFN-gamma released.	Measures quantity of IFN-gamma released from cells after cultivation with two antigens seen in tuberculosis: ESAT-6 and CFP-10.	Uses patients' whole blood to measure the release of IFN-gamma in response to TB antigens ESAT-6, CFP-10, and TB7 and measures the amount of IFN-gamma released in IU/mL^3 using ELISA.	Isolates the peripheral blood mononuclear cells which are incubated with ESAT-6 and CFP-10, and the ELISpot then detects activated effector T cells that secrete IFN-gamma.

the upper lobe, fibronodular disease in the upper lobe, or calcified granulomas. Individuals with abnormal radiographs or normal radiographs with pulmonary symptoms should undergo further analysis.[4,2] They should have three sputum specimens collected for acid-fast bacilli smear and culture in 8- to 24-hour intervals with at least one specimen in the early morning in order to rule out active tuberculosis. If patients are at moderate-to-high risk for TB, nucleic acid amplification should be performed on at least one specimen.[8]

Treatment. HIV-negative adults with LTBI should be treated with isoniazid preventive therapy (IPT) for nine months or, for individuals who have been recently infected, three months of weekly isoniazid and rifapentine.[9]

INTERFERON-GAMMA-RELEASE ASSAYS (IGRA)

Timeline of IGRA approvals. Before 2001, the TST was the only available test for LTBI. However, in that year the Centers for Disease Control and Prevention (CDC) introduced the first IGRA: QuantiFERON TB (Table 1). This blood test (and those to follow) measures the cell-mediated immune response by incubating the serum with mycobacterial antigens and then determining the IFN-gamma released. In 2005, the United States Food and Drug Administration (FDA) approved QuantiFERON Gold, which measures quantity of IFN-gamma released from cells after cultivation with two antigens seen in tuberculosis: ESAT-6 and CFP-10. These antigens are also seen in other atypical mycobacteria, which can cause a false-positive test result.[3] In 2007, QuantiFERUM Gold-in-Tube (QFT-GIT) was approved. It uses patients' whole blood to measure the release of IFN-gamma in response to TB antigens ESAT-6, CFP-10, and TB7 and measures the amount of IFN-gamma released in IU/mL^3 using ELISA. In 2008, the T-SPOT.TB assay was introduced. It isolates the peripheral blood mononuclear cells which are incubated with ESAT-6 and CFP-10, and the ELISpot, then detects activated effector T cells that secrete IFN-gamma.[3,10]

Advantages. Similar to the TST, IGRAs are also safe in both children and pregnant women.[5,6] The IGRAs also have a number of advantages when compared to the TST. They require just one patient visit for blood draw compared to the two visits required for a one-step TST. Unlike the TST, they do not cause a booster phenomenon, nor are they affected by BCG or most environmental mycobacteria.[4] IGRAs retain their high specificity, especially QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube. Out of all the IGRAs, T-SPOT.TB seems the most sensitive.[3] Additionally, results of IGRAs are usually available within 24 hours versus the 48 to 72 hours for the TST, and the laboratory test is unaffected by healthcare worker bias.

Limitations. The IGRAs have their own set of limitations as well. For example, the blood samples must take place within the strict timeframe of 8 to 30 hours after collection. Additionally, limited data exist on their use in children under five years old, individuals with recent TB exposure, immunocompromised individuals, and those who must undergo serial testing.[4] Further, their cost is higher than the TST. Additionally, most of the current studies of IGRAs take place in high-income countries, so their application in lower income countries is problematic. In fact, the World Health Organization has recommended against their use in low- and medium-income countries. Further, IGRAs have a lower sensitivity in high-burden settings such as those with higher population of TB or HIV.[10] Also, similar to the TST, IGRAs do not distinguish between recent and remote infections and have a low predictive value for active tuberculosis.[4,10] Finally, both TST and IGRAs have a lower sensitivity when testing People Living with HIV/AIDS (PLWHA) as both tests require a greater immune response.[10]

Work-up. When individuals test positive with IGRAs, they should undergo the same work-up as those who test positive with TST: Chest radiograph and (if positive) followed by sputum smear/culture x3 to rule out active tuberculosis.[3]

Treatment. IPT is established as protective only among TST-positive individuals. Additionally, spontaneous reversion of positive IGRA is common if the TST is negative. Thus, treatment of TST-/IGRA+ individuals is not recommended unless that individual was at higher risk of tuberculosis.[10]

RECOMMENDATIONS

IGRAs are growing to be the preferred test of choice based on their convenience (fewer trips to the doctor's office), lack of bias in interpreting tests, faster test results, lack of a booster phenomenon, and being unaffected by the BCG vaccine. However, these tests have their drawbacks in that they are more costly and less researched than the TST. Neither the TST nor the IGRAs provide acceptable results for people with active tuberculosis or PLWHA, so more research is needed in this area.

TABLE 2. Comparison of tuberculin skin testing and interferon-gamma-release assays

TST	IGRAS
2 office visits (or 4 if 2-step PPD)	1 office visit
Can cause booster phenomenon	No booster phenomenon
Can result in false positive with BCG vaccine	Unaffected by BCG vaccine
Subject to healthcare worker bias interpretation	Not subject to bias
Take 48–72 hours for results	Take 24 hours for results
Lower cost	Higher cost
More data on use in children	Limited data on children under 5 years old
Does not differentiate between recent and remote infections	
Has a lower predictive value for active tuberculosis	
Sensitivity is lower in PLWHA as greater immune response is required	

REFERENCES

1. Centers for Disease Control and Prevention (CDC). *Tuberculosis: Data and Statistics. 2012.* http://www.cdc.gov/tb/statistics/default.htm?s_ cid=fb1804. Accessed on April 26, 2014.
2. Pai M, Menzies D. Diagnosis of latent tuberculosis infection (tuberculosis screening) in HIV-negative adults. *UpToDate*. 2014 March. http://www.uptodate.com.lecomlrc.lecom.edu/contents/diagnosis-of-latent-tuberculosis-infection-tuberculosis-screening-in-hiv-negative-adults?source=preview&anchor= H27&selectedTitle=1~150#H27. Accessed on April 21, 2014.
3. Matthews EK, Shecter R. Interferon-gamma-release assays: a guide to clinical use in dermatology. *J Am Osteopath Coll Dermatol*. 2013;25:13–15.
4. Centers for Disease Control and Prevention (CDC). *Latent Tuberculosis Infection: A Guide for Primary Healthcare Providers*. 2013 April. http://www.cdc.gov/tb/publications/LTBI/diagnosis.htm#3. Accessed on April 25, 2014.
5. Adams LV, Starke JR. Tuberculosis disease in children. *UpToDate*. 2014 March. http://www.uptodate.com.lecomlrc.lecom.edu/contents/tuberculosis-disease-in-children?source=search_result&search= tuberculosis+testing+HIV+positive&selectedTitle=1~150#H11. Accessed on April 26, 2014.
6. Friedman LN, Tanoue LT. Tuberculosis in pregnancy. *UpToDate*. 2014 March. http://www.uptodate.com.lecomlrc.lecom.edu/contents/tuberculosis-in-pregnancy?source=search_result&search= tuberculosis+testing+pregnancy&selectedTitle=1~150#H18. Accessed on April 26, 2014.
7. Maartens G. Epidemiology, clinical manifestations, and diagnosis of tuberculosis in HIV-infected patients. *UpToDate*. 2014 March. http://www.uptodate.com.lecomlrc.lecom.edu/contents/epidemiology-clinical-manifestations-and-diagnosis-of-tuberculosis-in-hiv-infected-patients?source=see_link#H5989329. Accessed on April 26, 2014.
8. Bernardo J. Diagnosis of pulmonary tuberculosis in HIV-negative patients. *UpToDate*. 2014 April. http://www.uptodate.com.lecomlrc.lecom.edu/contents/diagnosis-of-pulmonary-tuberculosis-in-hiv-negative-patients?source=see_link#H8. Accessed on April 26, 2014.
9. Horsburgh CR. Treatment of latent tuberculosis infection in HIV-negative adults. *UpToDate*. 2014 March. http://www.uptodate.com.lecomlrc.lecom.edu/contents/treatment-of-latent-tuberculosis-infection-in-hiv-negative-adults?source=search_result&search=ltbi+treatment&selectedTitle=1~147#H13. Accessed on April 25, 2014.
10. Trajman A, Steffen RE, Menzies D. Interferon-gamma release assays versus tuberculin skin testing for the diagnosis of latent tuberculosis infection: an overview of evidence. *Pulm Med*. 2013. doi: 10.1155/2013/601737.